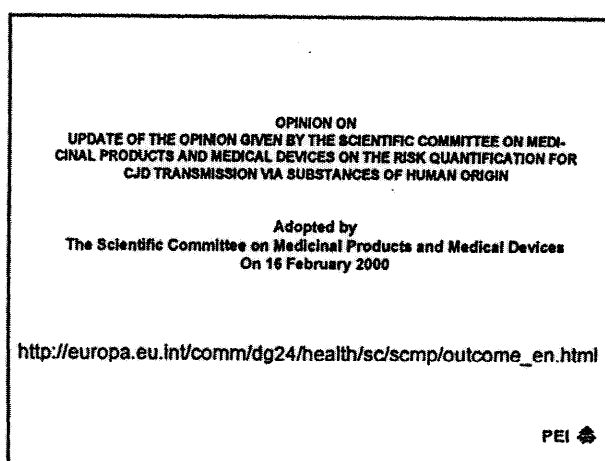
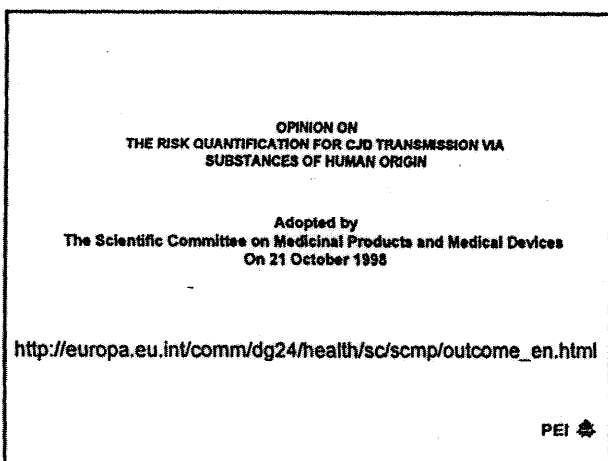
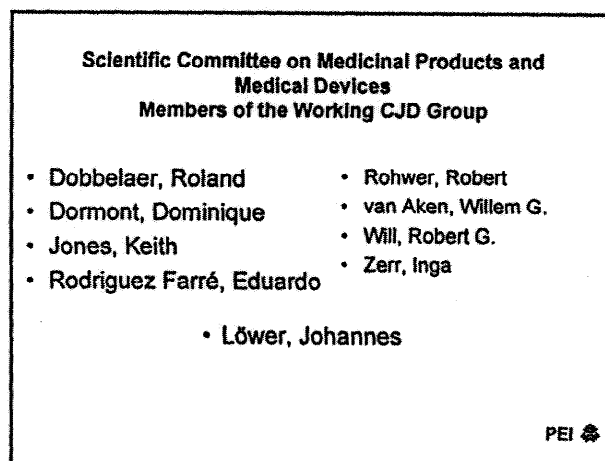
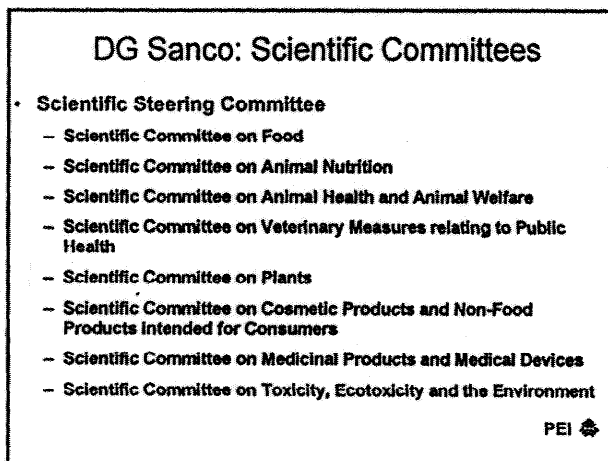
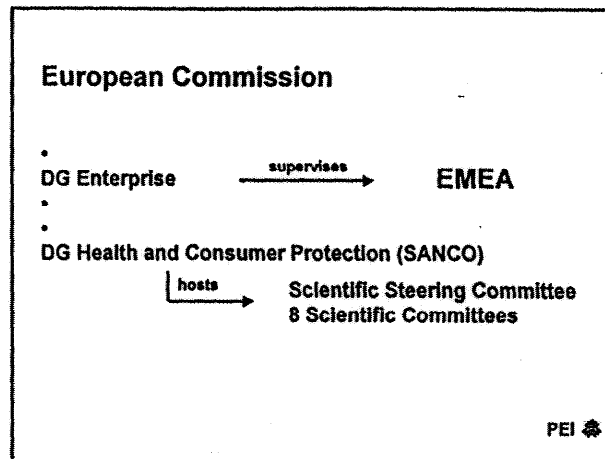
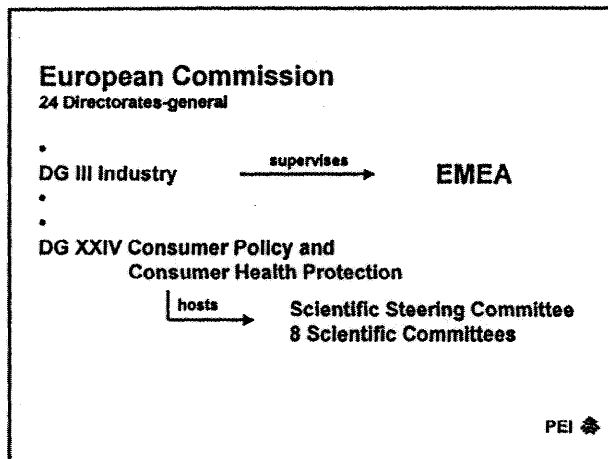


June 1, 2000

11:35 a.m. New-variant CJD and Blood Safety in the European Union. Potential human exposure to BSE, national and EC surveillance activities and public policies concerning blood
J. Löwer, MD
 Paul Ehrlich Institute
 Langen, Germany

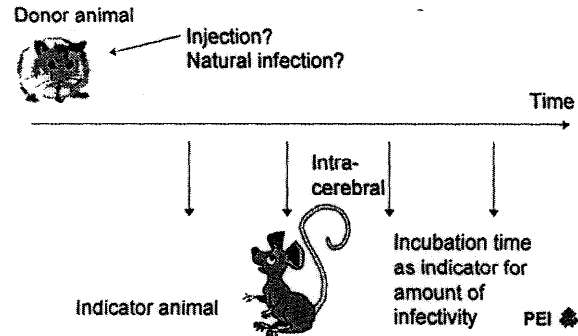


Case control studies

- Kondo 1982: 1 case vs. 3 controls
- Davanipur 1985: odds ratio 0.6
- Esmonde 1993: 14% cases vs. 19% controls
- van Duijn 1998: no significantly increased risk of CJD related to past medical history including surgery and blood transfusion, only significant risk factor: family history of dementia

PEI

EXPERIMENTAL STUDIES ON TSE INFECTIVITY IN BLOOD AND ITS COMPONENTS



PEI

EXPERIMENTAL STUDIES ON TSE INFECTIVITY IN BLOOD AND ITS COMPONENTS

- Species barrier
- Route of administration
- Agent strain (scrapie strains, CJD)
- Amount of infectivity (dose)
- Definition of endpoint
- Tenacity of the agent
- Observation time
- Use of inbred animals
- Genotype of indicator animal

PEI

- Donor animals naturally infected
- Donor animals and indicator animals: same species

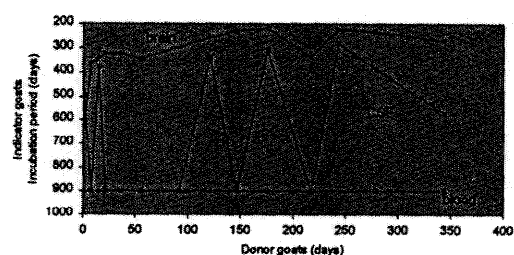
No published studies

PEI

author	TSE strain, route of administration	donor species	tissue	indicator amount of material, route of administration	animal species	remarks
Hedlow, W.J. (1974)	scrapie Chandler strain (derived from Chester sheep) i.e. $10^{7.7}$ mouse i.c. LD ₅₀ s.e. $10^{7.7}$ mouse i.c. LD ₅₀ i.e. $10^{8.4}$ mouse i.c. LD ₅₀	goats (Swedish breeding)	10% blood clot (whole blood?)	30 μ l i.c.	Swiss mice	scrapie, include time course studies, no infectivity found in blood clots
Wells, G.A.H. (1990) Wells, G.A.H. (1996)	BSE (homogenate of brain stems of 75 cases of BSE) 100 g single oral dose	Fleisch/Polstein male calves	10% buffy coat	20 μ l i.c. and 100 μ l i.p.	PR1 mice of C57BL/6J mice	time course study, no infectivity to buffy coat up to 22 months post inoculation, study not yet completed

PEI

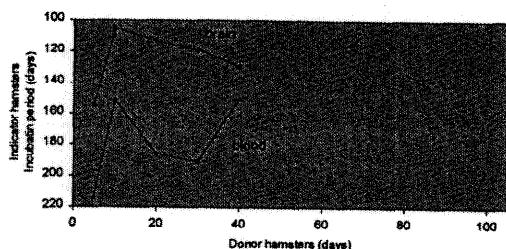
Tissue infectivity in scrapie goats



Pattison, I.H., Millson, G.C. Distribution of the scrapie agent in the tissues of experimentally inoculated goats. J.Comp.Path. 72, 233-244, 1962
Donor goats: i.c.
Indicator goats: i.c. 1 ml whole blood

PEI

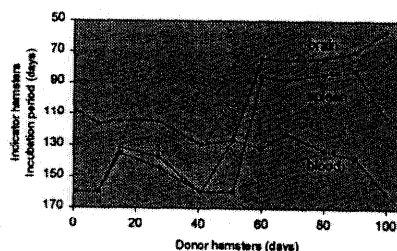
Infectivity of P_{215S} in scrapie hamsters



Diringer, H. Sustained viremia in experimental hamster scrapie. Arch.Virol. 82,105-109,1984
Donor hamsters: i.p.
Indicator hamsters: i.c. P_{215S} (equivalent to 2 ml blood)

PEI

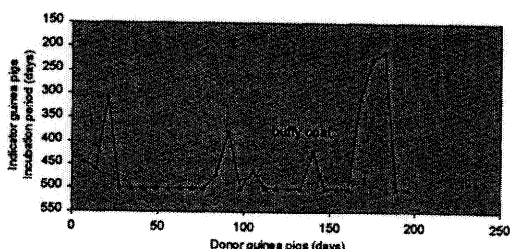
Infectivity of P_{215S} in scrapie hamsters



Casaccia, P. et al. Levels of infectivity in the blood throughout the incubation period of hamsters peripherally injected with scrapie. Arch.Virol. 108, 145-149, 1989
Donor hamsters: i.p.
Indicator hamsters: i.c. P_{215S} (equivalent to 0.2 ml blood)

PEI

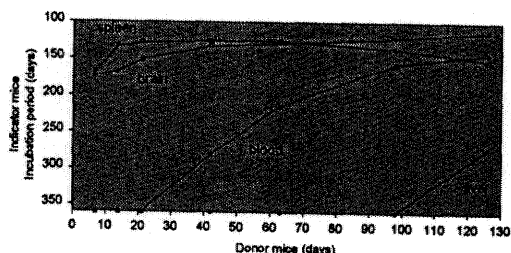
Infectivity of buffy coat in CJD Guinea pigs



Manuelidis, E.E., Gorgacz, E.J., Manuelidis, L. Viremia in experimental Creutzfeldt-Jakob disease. Science 200, 1069-1071, 1978
Donor guinea pigs: i.c.
Indicator guinea pigs: 0.1 ml i.c.+s.c.+i.m.+i.p. buffy coat

PEI

Tissue infectivity in GSS mice



Kuroda, Y., Gibbs, C.J. Jr., Amyx, H.L., Gajdusek, D.C. Creutzfeldt-Jakob disease in mice: persistent viremia and preferential replication of virus in low-density lymphocytes. Infect.Imm. 41, 164-181, 1983
Donor mice: i.c.
Indicator mice: i.c. buffy coat, i.p. serum and erythrocytes

PEI

Conclusions from animal experiments

- No infectivity in blood of Kuru and CJD patients demonstrable. Iatrogenic CJD? nvCJD? Use of transgenic mice?
- Low level of infectivity in animal models, best demonstrable in small (inbred?) rodents. Titer 1 to 10 IU/ml (HIV, HCV, HBV >10⁵)
- TSE agent and peripheral leukocytes? No parallelism between infectivity in spleen and blood

PEI

Assessment of risk of transmission by blood: CJD vs. vCJD

CJD

- No epidemiological evidence
- Extrapolation of animal data possible?
- PrP^{Sc} not found in peripheral tissues
- Predominantly in older individuals

vCJD

- Insufficient epidemiological data
- Extrapolation of animal data possible?
- PrP^{Sc} found in lymphoreticular tissue
- Predominantly in young individuals (mean age at onset: 28 yrs.)

PEI

Assessment of risk of transmission by blood: CJD vs. vCJD

- | CJD | vCJD |
|---|--|
| <ul style="list-style-type: none"> • Occurrence all over the world (1 case per million per year) | <ul style="list-style-type: none"> • Occurrence predominantly in UK (57 confirmed, 13 probable) |

Risk for vCJD: Residency in UK

USA, Canada and others: Exclusion of donors who stayed cumulatively at least six months in UK between 1980 and 1996.

PEI ☘

Germany

Ministry of Health

is advised by →

"Arbeitskreis Blut"
(Blood Advisory Board)
managed by the Robert Koch-Institut,
Berlin

supervises →

Paul-Ehrlich-Institut
(PEI)
Plasma derived products, labile
blood components: Licensing,
batch control, hemovigilance

PEI ☘

Arbeitskreis Blut

Session of August 1999

- There are no new scientific data which may change the risk assessment regarding the transmission of vCJD by blood (28 yes, 1 abstention)
- The FDA measures cannot be transferred to Germany because of differences in basic assumptions (29 yes)

PEI ☘

Arbeitskreis Blut

Session of August 1999

- A survey of blood donors regarding their pattern of travels to UK should be performed (13 yes, 14 no)
- UK Citizens should be excluded from donation (9 yes, 11 no, 8 abstentions)

PEI ☘

Questions:

Does the exclusion of donors who stayed for some time in UK contribute to the safety of the blood supply?

What is the risk to acquire vCJD in the EU outside UK?

How does the exclusion of donors influence the blood supply quantitatively and qualitatively?

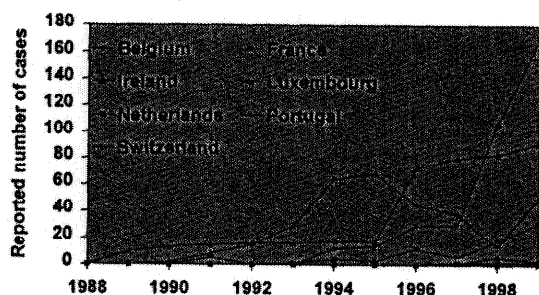
PEI ☘

What is the risk to acquire vCJD in the EU outside UK?

- Export of live cattle from UK to continental Europe during the BSE epizootic (France, Netherlands)
- Export of bovine material (meat, meat and bone meal, others) from UK to continental Europe during the BSE epizootic (France, Netherlands)
- Endogenous BSE in continental Europe (Switzerland, Portugal, France, Netherlands and others)

PEI ☘

Indigenous BSE Cases



Figures published by Office International des Epizooties O.I.E.

PEI

What is the risk to acquire vCJD in the EU outside UK?

- vCJD cases outside UK: France, Ireland

What is the relative risk of many people staying 60 months (5 years) or 600 months (50 years) in Germany (France, Portugal) versus a small percentage staying 6 months or longer in UK?

PEI

What is the risk to acquire vCJD in the EU outside UK?

What is the relative risk of staying 60 months (5 years) or 600 months (50 years) in Germany (France, Portugal) versus staying 6 months in UK?

If we guess that the relative risk is close to zero we may exclude donors who have visited UK, but how should we react if numbers of vCJD cases increase outside UK?

Extension of the measure is not feasible.

Hope for screening tests.

PEI

How does the exclusion of donors influence the blood supply quantitatively and qualitatively?

Reduction of the number of donors (6 months as exclusion criterion \Rightarrow reduction by about 2.5%)

Replacement by first-time donors with increased risk for blood-borne infections: HIV, HBV, HCV

PEI

How does the exclusion of donors influence the blood supply quantitatively and qualitatively?

How many HIV infections are we ready to accept in exchange to the reduction of the risk from exposure to BSE in UK?

PEI

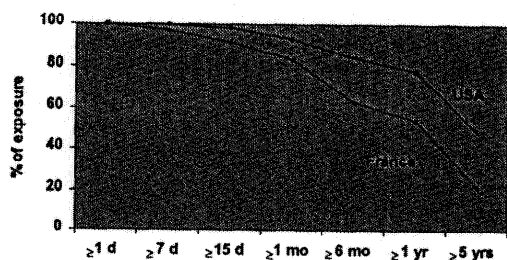
SCMPMD Opinion of 16 February 2000

Three sets of data have to be collected and evaluated:

- The travel pattern of European donors which may differ between Member States.
- The exposure to UK bovine derived material in food between 1980 and 1996 in different Member States.
- The prevalence of HIV, HBV and HCV in first time donors in different Member States.

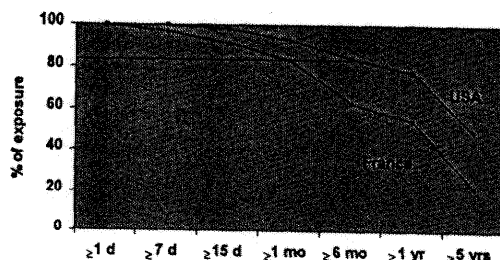
PEI

Cumulative exposure risk



PEI

Cumulative exposure risk



PEI

SCMPMD Opinion of 16 February 2000

Three sets of data have to be collected and evaluated:

- The travel pattern of European donors which may differ between Member States.
- The exposure to UK bovine derived material in food between 1980 and 1996 in different Member States.
- The prevalence of HIV, HBV and HCV in first time donors in different Member States.

PEI

Summary on donor deferral

- No decision in the European Union so far
- Survey initiated
- European harmonisation
 - CJD expert group of BWP and CPMP (EMEA)
 - Working group "Blood and CJD" of the SCMPMD
 - others

PEI

SCMPMD Opinion of 16 February 2000: Leukofiltration

In contrast to the classical forms of CJD, infectivity may be present in peripheral blood of vCJD cases (as extrapolated from models of small laboratory animals with a peripheral distribution of the pathological form of the prion protein similar to that in vCJD patients) and this infectivity may be predominantly associated with white blood cells (again inferred from models of small laboratory animals).

PEI

SCMPMD Opinion of 16 February 2000: Leukofiltration

Caveats:

- lack of experimental proof of reduction of TSE infectivity
- cell types carrying TSE infectivity unknown
- degree of removal of those cells unknown
- effect of different types of filters unknown
- lack of validation

PEI

**SCMPMD Opinion of 16 February 2000:
Leukofiltration**

In the meantime, it might be advisable to introduce leukofiltration as a precautionary step, as it is assumed that it will contribute to diminishing infectivity in blood. A recommendation for the general use of leukofiltration would be in line with the belief that many if not all transfusion recipients would benefit from the removal of white blood cells for other reasons.

PEI 